Psoriatic arthritis – expanding options, exciting times?

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In the last decade, the advent of novel medicines and the implementation of disease activity targeted strategies in the treatment of rheumatoid arthritis (RA) have transformed expectations amongst health care professionals and patients alike. Outcomes are improved, function is often maintained, remission is achieved in a proportion of patients and co-morbidities are reduced. Can the same be said for psoriatic arthritis (PsA) over this time period? Recalling the old school master's report card – "could do better" might be a not unreasonable response.

PsA comprises a heterogeneous clinical presentation that sets out a number of challenges in terms of pathogenetic explanation and therapeutic management. Patients will variously exhibit synovitis, enthesitis and osteitis and will usually also have skin disease across the range of cutaneous and nail manifestations of psoriasis. The radiographic appearances are of complex bone remodeling with evidence of bone loss, new bone formation and entheseal reactions, often co-existing in a given patient or joint. Sophisticated imaging, particularly Magnetic Resonance Imaging (MRI) and ultrasound, imaginatively applied has refined considerably out understanding of the clinical phenotype of disease and increasingly we now recognize that musculoskeletal involvement across the psoriasis spectrum is broader than previously considered and that such recognition may carry prognostic significance[1]. Thus aggressive pro-active interventions with an emphasis on early recognition, detection and treatment of PsA likely represents an attractive 'next step forward'. That Tumor Necrosis Factor (TNF) inhibition has delivered significant progress is not in dispute – indeed it should be celebrated in PsA just as it has been in RA. TNF inhibition delivers robust responses in many PsA patients and clearly reduces radiographic progression and functional decay. However around half of Tumor Necrosis Factor inhibitors (TNFi) treated patients will discontinue treatment over 5 years[2]. As such we are faced with a life-long disease in which existing guidelines, e.g. those provided by European League Against Rheumatism (EULAR), suggest that the next step upon TNFi failure remains re-cycling of agents of the same general mode of action.

Clinical heterogeneity thus poses two rather fundamental challenges to the clinician. First, is the pathogenesis of each tissue lesion and location mediated via common or disparate pathways? Second, and predicated upon this notion, should we have similar expectations of a given intervention in each tissue compartment?

There is now abundant evidence implicating Interleukin-17 (IL-17) dependent immune pathways in the pathogenesis of cutaneous psoriasis lesions[3]. The presence in lesions of several members of the IL-17 superfamily is established and the effector functions mediated via the IL-17 receptor family are consistent with the pathologic changes observed in tissues. The critical hierarchical position of the pathway is strongly suggested by the remarkable magnitude and frequency of responses seen upon IL-12/23(p40), IL-17A, or IL-17RA blockade in patients with psoriasis[4]. Mode-of-action studies similarly suggest that the IL-17 pathway occupies a pivotal functional position in the hierarchy of the pathologic lesion[5]. There is also evidence of IL-17 pathway expression in PsA – with circulating and tissue Th17 (CD4 and CD8) cell subsets clearly identified with higher frequency and evidence that IL-17 can mediate activation of relevant tissue cells including synovial fibroblasts, osteoclasts, neutrophils and the like. Clinical targeting of IL-12/23(p40), and more recently of IL-17A is also consistent with a functional role for such pathways in manifestations of disease. Ustekinumab is now approved for use in PsA and phase III trials are ongoing based on encouraging phase II datasets for agents targeting the IL-17 pathway, such as secukinumab and brodalumab.

This development is very exciting and offers real hope of therapeutic expansion in terms of available modes of action. However an objective appraisal of the

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currently observed magnitude of response in PsA to these new agents is perhaps a little disappointing when one considers the significantly superior impact on skin as opposed to musculoskeletal presentations. For reasons as yet unclear, we are not achieving the very high hurdle responses in musculoskeletal presentations as we are in cutaneous disease (e.g. consider the impressive proportion of PASI90 and PASI100 responders with attendant improvements in quality of life). This is unlikely to reflect some functional defect on the part of the medicines that target the IL-17 pathway since they are clearly effective and powerful agents in the skin – it is however possible that bioavailabilty in relatively avascular tissues such as the enthesis could affect their potential for local inhibition.

Such discrepancies may reflect the outcome measures currently available to determine impact in PsA, many of which were developed for use in RA and have been borrowed or modestly adapted for application in PsA. The important work of Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in developing new outcome measures and composite scores will likely be of assistance in this respect. One caution on the use of composite measures that include synovial enthesial and cutaneous measures together with global evaluations of 'well being', might be the risk of missing tissue specific effects. Thus if composite measures are used to evaluate an agent in which only one tissue might be expect to respond one could erroneously conclude no value in an agent. A further possibility is that there are simply ceiling effects operating for a given outcome(s) measure – e.g. permanent loss of articular function which cannot be recovered to the equivalent level of 'PASI100', or pain arising from secondary Osteoarthritis (OA), or fibromyalgia which 'contaminates' the reporting of inflammatory manifestations of disease.

These clinical response discrepancies may however offer a more fundamental insight to tissue specific pathways whereby the contribution of given cytokines is distinct for a given tissue across the PsA spectrum. This is not unreasonable since the immune system has adapted over eons to hone tissue responses for optimal host defence based on the nature of microbial insult in different organs and the sensitivity of local structures to aggressive immune reactions. Thus going forward it will be imperative to formally evaluate each tissue in turn upon clinical inhibition and perhaps one should be judicious in extrapolation from skin to musculoskeletal tissues and vice versa.

Taken together, we are clearly now embarked upon a new journey in the generation of therapeutic options for PsA, which are increasingly diverging from those used for RA. New biologic modes of action defined above are here already, or emerging. Small molecule inhibitors that recover an anti-inflammatory cytokine milieu e.g. apremilast via inhibition of phosphodiesterase type 4 inhibitor (PDE4), or directly target cytokine receptor signaling pathways, particularly via blockade of Janus kinases (JAK) signaling, are also approved, or en route. How best to use such agents, in what order and in what strategic approach remains uncertain. Determining the optimal outcome measures to inform drug development and routine practice decisions will also require elucidation. Can we develop biomarkers to further enrich for responses? Exciting times indeed but still a work in progress.

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REFERENCES

1. Tan AL, McGonagle D. Psoriatic arthritis: correlation between imaging and pathology. Joint Bone Spine 2010;77(3):206-211. doi: 10.1016/j.jbspin.2009.09.011.
2. Glintborg B, Ostergaard M, Krogh NS, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis Rheum 2013;65(5):1213-1223. doi: 10.1002/art.37876.
3. Frleta M, Siebert S, McInnes IB. The interleukin-17 pathway in psoriasis and psoriatic arthritis: disease pathogenesis and possibilities of treatment. Curr Rheumatol Rep 2014;16(4):414. doi: 10.1007/s11926-014-0414-y
4. Sobell JM, Leonardi CL. Therapeutic development in psoriasis. Semin Cutan Med Surg. 2014;33:S69-72. doi: 10.12788/j.sder.0098.
5. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol. 2014;32:227-55. doi: 10.1146/annurev-immunol-032713-120225